REMARKS

Upon entry of the present amendment, Claims 1-37, 77, 83-94, 97-108,119, 121, and 123 will be pending in the application. Claims 1-37, 77, 84-87, 93, 94, 97 and 101-108 were previously withdrawn. Claim 122 is presently cancelled and claims 38-76, 78-82, 96, 109-118, 120, and 124-130 were previously cancelled.

The Examiner is requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

1. CLAIM OBJECTIONS

Claim 122 is objected to because of the following informalities: Claim 122 depends from cancelled Claim 120.

Claim 122 is cancelled rendering the objection moot. Withdrawal of the objection is requested.

2. REJECTION UNDER 35 U.S.C. § 103 – HERMAN & SLAVIN-CHIORINI

Claims 83, 88-92, 98-100, 119, and 121-123 stand rejected under 35 U.S.C. § 102(e) as allegedly unpatentable over Herman (U.S. Pub. No. 2005/0069549, published March 31, 2005, filed January 14, 2003; cited in the PTO 892 form of 11/7/2006 in view of Slavin-Chiorini et al. (Int. J. Can. 53:97-103(1993)) This rejection is respectfully traversed.

The present claims are not obvious over Herman and Slavin-Chiorini as these documents fail to provide for all of the claimed features. Namely, the combination fails to provide the presently claimed nucleic acid encoding a monomer unit of a recombinant

antibody-based dimeric molecule, where the nucleic acid encodes an antigenic unit, a dimerization motif and a targeting unit operably connected to encode the monomer unit. And the rejection fails to provide an apparent reason based on the cited documents or the general knowledge in the art as to how or why a person of ordinary skill would modify these documents to include the missing subject matter in a fashion that would recreate the present claims.

To establish a *prima facie* case of obviousness predicated on a combination of documents, the combination must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Or, if the documents are missing claimed features, there must be some apparent reason either in the documents or the general knowledge in the art by which to modify the documents to include the missing subject matter in the fashion claimed. See *Id.* and *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 USPQ2d 1385, 1396 (2007) (obviousness includes determining whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue). And MPEP § 2143 states that "[t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious," which should be made explicit and must be anchored by a rational underpinning, as directed by *KSR Int'l Co. v. Teleflex Inc.* This burden is not met in the present rejection based on Herman in view of Slavin-Chiorini.

The antibody-like format of the dimeric expression products encoded by the presently claimed nucleic acids are not the same as the antibodies and antibody variants found in the Herman and Slavin-Chiorini documents.

The presently claimed constructs encode the monomer units of homodimeric proteins. Each monomer includes a targeting unit and an antigenic unit – these are positioned in each end of the encoded monomer polypeptide and are hence separated by the recited components from an antibody (hinge region and Cy3 domain etc. but not a CH2 domain). It is, however, important to understand that the encoded constructs according to the present claims need not include an antigen binding site of an antibody. Rather, the important functionalities of the two units (the antigenic unit and the targeting unit) are their ability to function as an antigen (which can induce antibodies) and to target the homodimeric molecule to a relevant cell (for instance an antigen presenting cell). The homodimeric molecules are useful as vaccine agents, and this is also the case for the claimed nucleic acids (when used in nucleic acid vaccination) but the nucleic acids may also be used in expression vectors for recombinant production of the homodimeric molecules.

With respect to the Herman document, on page 6 of the Office Action the Examiner alleges that Herman discloses "...multispecific ligands comprising at least two different binding specificities for different target ligands comprising any combination of one or more antibody fragments or recombinant reconstructions (scFvs) of antibodies including tetraspecific antibody formats and fusion of the antibody to other functional moieties (e.g., toxins, cytokines,...)", as well as nucleic acids and vectors encoding the same. The Herman document, however, does not enable nucleic acids encoding any and all multispecific constructs. In particular, Herman does not at all address production of antibody-based dimeric molecules comprising two monomer units encoded by the same nucleic acid – such molecules will not be "multispecific" as this term is used in

Herman. What Herman might fairly be considered to disclose relates to various specific constructs based on bispecific antibodies (see, e.g., paragraphs [0011] and [0061]). Bispecific antibodies are based on heterodimerization of two non-identical monomer units where one monomer contains an antigen-binding region from one antibody and the other monomer contains an antigen-binding region from a different antibody.

Indeed, the U.S.P.T.O finds that the Herman specification "discloses a method of making bispecific antibodies, minibodies diabody [sic] where one or two diabody molecules are heterodimerized by creating a fusion protein with the CL and CH1 immunoglobulin constant domains" (emphasis added). See page 4 of the August 21, 2008 Office Action in corresponding patent application U.S. Pat. Appl. Ser. No. 10/501,453, now in appeal.

To conclude, as correctly pointed out by the Examiner, the Herman document discloses nucleic acids which are useful for preparation of multispecific (bispecific) constructs. It is very hard to see that a skilled person would readily combine such with, for example, the Slavin-Chiorini disclosure (discussed below), which is focused on production of monoclonal antibody variants, which are by nature monospecific.

With respect to the Slavin-Chiorini document, on page 8 of the Office Action the Examiner alleges that "Slavin-Chiorini discloses the long-felt need to obtain recombinant Ig molecules with rapid plasma clearance and little or no ability to elicit a HAMA response for use in diagnostic or therapeutic regimens, and that by deleting the CH2 domain of an intact Mab, the ordinary artisan could reasonably expect to obtain these results for murine and chimeric antibodies" (emphasis added). First, to state that there is a long felt need for Ig molecules with rapid plasma clearance seems to be an

overinterpretation of the contents of Slavin-Chiorini. What the document discloses is that certain radiolabeled monoclonal antibodies exhibit a drawback by having slow plasma clearance; cf. the first paragraph of Slavin-Chiorini. So, Slavin-Chiorini suggests provision of high-clearance rate mABs where the CH2 domain is deleted, but the purpose is tightly linked to the problems encountered when maintaining a level of radioactivity in plasma, if the radiolabeled antibodies have too low a clearance rate. Slavin-Chiorini in no way suggests that a high plasma clearance rate is a generally useful feature.

A rapid plasma clearance rate is exactly the opposite of what is aimed at in the present claims and specification, wherein a prolonged serum half-life (i.e., slow plasma clearance) of the antibody-like expression products is desired – this is independent of whether the presently claimed nucleic acids are used for nucleic acid vaccination or for recombinant production of molecules, which in turn are used in therapy. Simply put, the plasma concentration of any drug is dependent on the drug input and the clearance rate of the drug. For a nucleic acid vaccine, the "input" is the same as the expression rate: a plasmid is administered, and this plasmid effects expression of the protein, which is the true immunogen in the vaccine. If the expression products of the presently claimed nucleic acids are administered per se, the "input" is simply the amount of expression product administered per time unit.

One of the important issues when preparing a nucleic acid vaccine is to ensure a sufficient expression level of the expression product. Much work is and has been invested in the provision of effective expression plasmids and methods of obtaining sufficient transfection in order to obtain high level expression. However, it should be

needless to state that all such attempts at obtaining a high expression level of nucleic acid vaccine plasmid are directly counteracted if the expression product itself (i.e., the encoded protein) has a rapid clearance rate.

To underscore this argument, the enclosed document by Wolff and Budker discusses various techniques to increase the long-term expression levels of administered naked DNA for various applications; e.g., as genetic vaccines. Specifically, the Wolff and Budker document notes that "[a]lso, contrary to common belief, long-term gene foreign expression from naked plasmid DNA (pDNA) is possible..." and "[w]ith the advent of intravascular and electroporation techniques, its major restriction – poor expression levels – is no longer limiting...." On the other hand, designing a nucleic acid vaccine which encodes a recombinant Ig molecule which is recognized as having a rapid clearance rate form plasma once it has been expressed (as in the Slavin-Chiorini document) would defeat the purpose of a prolonged high-level expression of the nucleic acid, lessening the time period during which the immune system is exposed to the vaccine molecule.

When preparing a protein-based vaccine, is should go without saying that the skilled artisan will naturally avoid production of vaccine agents which will require administration of increased dosages – this would however be the consequence of designing a molecule having an increased clearance as those suggested by Slavin-Chiorini.

Consequently, in the art of nucleic acid-based vaccines, a prolonged high level of expression is sought and in traditional vaccines it would be avoided to increase the plasma clearance of an immunogen. So, to conclude, a person skilled in the art

desiring to produce a vaccine would, when studying the Slavin-Chiorini document, clearly be dissuaded from deleting the CH2 domain from any construct taught in Herman, because this would counteract the effect of having a high expression level. Further, the combination of Herman and Slavin-Chiorini does not appear to be obvious for the simple reason that Herman addresses production of multispecific antibody variants where Slavin-Chiorini addresses the production of monospecific antibody variants.

Reconsideration of the claims and withdrawal of the rejection are respectfully requested.

3. CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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enclosure: Abstract of "The mechanism of naked DNA uptake and expression" by Wolff JA, Budker V. (3 pages)

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